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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/643,801	08/18/2003	Sanjay Bhanot	RTS-0678US (058823-0110)	4755

71476 7590 04/18/2008

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
04/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/643,801	BHANOT ET AL.	
	Examiner	Art Unit	
	J. E. Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,11-18,22-40,44 and 49-60* is/are pending in the application.

4a) Of the above claim(s) *18,22,25-31,33-40 and 49-57* is/are withdrawn from consideration.

5)☒ Claim(s) *1,3-9,11-17,22,44 and 58-60* is/are allowed.

6)☒ Claim(s) *23,24 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/20/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 1/30/2008.

The amendment filed 1/30/2008 is acknowledged and has been entered.

Claims 1, 3-9, 11-18, 22-40, 44 and 49-60 are currently pending in the application and are addressed herein.

Election/Restrictions

1. It is noted that claims 1, 3-9, 11-17, 22, 44 and 58-60 were previously indicated as being allowable; however, claims 18, 22-40 and 49-57 were subject to restriction.

2. Applicant's election of Group I, treating a cardiovascular disorder (claims 23, 24 and 32) in the reply filed on 1/30/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 18, 22, 25-31, 33-40 and 49-57 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/30/2008.

4. Claims 23, 24 and 32 are addressed below.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 7/20/2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 23, 24, 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the expression of diacylglycerol acyltransferase 2 using the oligonucleotide of claims 1, 3-9, 11-17, 22, 44 and 58-60, does not reasonably provide enablement for treating any disorder in a subject (claims 23, 32), let alone any cardiovascular disorder (claim 24). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> *Wands* states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method of treating any disorder in a subject, specifically including any cardiovascular disorder by administering to the subject an oligonucleotide compound that inhibits diacylglycerol acyltransferase 2 (DGAT2)

expression. As such, the invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims are very broad with respect to the disorders that are treated. Specifically, claims 23 and 32 encompass treating any disorder, while claim 24 encompasses treating any cardiovascular disorder.

The unpredictability of the art and the state of the prior art

It is a well accepted concept that in order for a method of inhibiting gene to be able to treat a disorder, the gene must, at a minimum, be correlated with the disorder. However, in the instant case, the claims encompass treating an extremely large genus of disorders by administering an oligonucleotide that inhibits DGAT2 expression. The genus of disorders encompassed by the claims includes disorders of which there is no correlation or association with DGAT2 expression. For instance, claims 23 and 32 encompass treating any disorder and claim 32 encompasses treating any cardiovascular disorder. Certainly, the genus that encompasses any disorder would include disorders that do not involve DGAT2. Furthermore, there are cardiovascular disorders of which there is no known association with DGAT2. For instance, primary tumors of the heart are very rare, with an estimated incidence of 0.0017% to 0.19% in unselected patients at autopsy (see Vaughan et al. Current Opinions in Cardiology, 2001; vol. 16, pages 195-200). Although Vaughan teaches a number of different genes which are associated with primary heart tumors (e.g., PRKAR1alpha, TSC-1 and TSC-2, PTC); however there is no

indication found in Vaughan or anywhere else in the art that indicates that DGAT2 may be associated with primary heart tumors. Furthermore, Melo et al. (Trends in Molecular Medicine, 2005) also reviews a number of cardiovascular diseases and the genetic therapies for their treatment (e.g., see Tables 2 and 3). For example, Melo teaches that vascular cell proliferation (Table 2), Myocardial infarction, Heart Failure and Congenital Heart Disease (Table 3) are cardiovascular disorders that are associated with specific genes; however, there is no indication that these cardiovascular disorders are associated with DGAT2. Furthermore, no association between DGAT2 and vascular cell proliferation, Myocardial infarction, Heart Failure or Congenital Heart Disease could be found in the prior art. Therefore, given the that there are a number of cardiovascular disorders which do not appear to have any correlation with DGAT2, further experimentation would required in order for the claimed methods to be enabled to their full scope.

Working Examples and Guidance in the Specification

The specification discloses a number of examples which indicate that oligonucleotides which inhibit the expression of DGAT2 can be administered in vitro and subcutaneously to mice (in vivo) and result in the inhibition of DGAT2 expression (e.g., see Examples 10, 15, 16, 18, 22; Tables 1, 2, 4, 8; etc.). However, the specification does not provide any guidance with respect to DGAT2 association with primary heart tumors, vascular cell proliferation, Myocardial infarction, Heart Failure or Congenital Heart Disease.

Quantity of Experimentation

Considering that the claims encompass treating any disease, and more specifically, any cardiovascular disease, which includes disease for which there is no known association with DGAT2 (e.g., primary heart tumors, vascular cell proliferation, Myocardial infarction, Heart Failure and Congenital Heart Disease), further experimentation would be required. Considering that there is no association between DGAT2 and these disorders, an enormous amount of additional experimentation would be required to enable the claimed methods for treating these disorders. For instance, first and association between DGAT2 and the disorder would have to be established. Then extensive experimentation, including in vitro testing and then animal testing, would be required and with no guarantee of success. Therefore, the additional experimentation that is required to enable the instant claims to their full scope is not routine and would constitute a significant advancement of the state of the art.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the nature of the invention, the breadth of the claims, the unpredictable nature of the invention as recognized in the prior art, the limited amount of working examples and guidance provided, and the high degree of skill required to practice the invention, it is concluded that the specification does not provide an enabling disclosure for the full scope of the instant claims. Therefore, additional experimentation is required before one of skill in the art could make and use the claimed invention to its full scope. The amount of additional experimentation required to perform the broadly claimed invention to its full scope is considered to be undue.

Conclusion

It is noted that with respect to the examination of rejoined process claims, MPEP 821.04 indicates:

> "If rejoinder occurs after the first Office action on the merits, and if any of the rejoined claims are unpatentable, e.g., if a rejection under 35 U.S.C. 112, first paragraph is made, then the next Office action may be made final where the new ground of rejection was necessitated by applicant's amendment (or based on information submitted in an IDS filed during the time period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p))."

In the instant case, rejoinder has occurred after the first Office action on the merits, and the rejoined claims are unpatentable for the reasons indicated herein. Therefore, it is proper to for the instant action to be made FINAL.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m. .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/
Primary Examiner, Art Unit 1635